

Revision of EPA 1-liners pertaining to the EPA Memorandum (1/13/89) was performed 12/12/89 (M. Silva).

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

SIMAZINE

Chemical Code # 000531, Tolerance # 00213
SB 950 # 129

August 11, 1986

Revised 10/8/87, 11/6/87, 6/15/88, 7/20/89, 8/6/90, 1/8/93, 10/8/93

I. DATA GAP STATUS

Combined (chronic + onco) rat: No data gap, possible adverse effect.

Chronic dog: No data gap, no adverse effect.

Oncogenicity, mouse: No data gap, no adverse effect.

Reproduction, rat: No data gap, no adverse effect.

Teratology, rat: No data gap, no adverse effect.

Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome mutation:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

All record numbers through 122625, volume 110 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T931008

Toxicology Summary updated by M. Silva on 6/15/88; J. Gee on 7/20/89; Kishiyama & Silva, 8/6/90; Kishiyama & Silva, 1/8/93; M. Silva, 10/8/93.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED CHRONIC TOXICITY/ONCOGENICITY - RAT

**** 067 067849** "Simazine Technical: 104-Week Oral Chronic Toxicity and Carcinogenicity Study in Rats," (Ciba-Geigy Corporation, Summit, NJ, 4/12/88). Simazine technical (Batch FL 850614; purity = 96.9%) was administered in diet to Crl: VAF/Plus CD (SD)Br rats at 0 (90/sex), 10 and 100 (80/sex) and 1000 ppm (90/sex) for 104 weeks. NOEL = 10 ppm (increased mortality in females; decrease in body weight gain at 1000 ppm--males and 100 & 1000 ppm females; decrease in food consumption at 1000 ppm in both sexes; a decrease in RBC, HGT and HCT was observed in females at 1000 ppm; in males an increase in relative brain, liver, testes/epididymus weights and a decreased heart and relative heart weight at 1000 ppm; in females an increased relative brain, kidney and liver weights at 1000 ppm). **Possible adverse effect** (The incidence of mammary carcinomas, fibroadenomas and cystic glandular hyperplasia was increased significantly at 100 and 1000 ppm in females; at 1000 ppm females showed an increased incidence of a rare kidney tubular adenoma). ACCEPTABLE. M. Silva, 6/8/88.

059 056393-056394 Interim report (1 year) for 067849. Gee, 11/6/87.

CHRONIC TOXICITY, RAT

034 021594 "Two-Year Dietary Feeding Study - Albino Rats," (Hazleton, Falls Church, VA, 1/15/60). Thirty/sex/dose were fed 0, 1, 10 or 100 ppm for 2 years. Purity of Simazine 50W = 49.9 %. Mean values rather than individual data, no histopathology on animals dying during study, notation of advanced autolysis in many animals dying during study, two tumors in control animals not examined. Nominal NOEL \geq 100 ppm. UNACCEPTABLE with insufficient information, no effect reported. (J. Gee, 5/1/85)

EPA 1-liner: No grade. Systemic NOEL > 100 ppm (HDT)

039 924023 Summary (1964) of 021594

Summary: The two studies in the rat do not agree but the study (volume/record # 067/067849), tested at a much higher dose level than the earlier study, showed the effect at the high dose. Therefore, the adverse effect from study 067849 is considered noteworthy. Silva, 6/88.

CHRONIC TOXICITY, DOG

** 064 067846 "Simazine - 52-Week Oral Feeding Study in Dogs," (Ciba-Geigy, 3/28/88). Simazine technical (FL #840988, purity = 96.5%) was administered in the diet for 52 weeks to Beagle dogs at 0, 20, 100, and 1250 ppm (4/sex/group). NOAEL > 1250 ppm (No significant dose related effects observed at any level). NOEL = 20 ppm (marginal effects on body weight gain at 100 ppm, slight effects in erythroid parameters) No adverse effect indicated. Initially reviewed as not acceptable (No MTD). CDFA requested the pilot study mentioned in the report. Considered possibly upgradeable with submission of the pilot study. M. Silva, 6/3/88. CDFA # 071979 in 213-076 was submitted for dose justification. CDFA Record # 071978 in 213-076, attachment 1, discusses the rationale for dose selection. The study is upgraded to ACCEPTABLE status with no adverse effect identified. (Gee, 7/19/89).

EPA 1-liner: NOEL = 20 ppm and LEL = 100 ppm (decreased body weight gain in females and reduced RBC, Hgb and Hct (1/13/89)).

076 071978 Copy of an internal memo of Ciba-Geigy discussing the rationale for dose selection for the 52-week study - CDFA # 067846. No worksheet. (Gee, 7/19/89).

076 071979 "Simazine Technical: Subacute Oral 13-Week Toxicity Study in Dogs." (Ciba-Geigy, Summit, NJ, 4/12/85, Report 85022) Simazine technical, Batch FL 840988, 97.5%; fed in the diet to 4/sex/group at 0 (diet), 200, 2000 or 4000 ppm for 13 weeks; body weight and food consumption were significantly lower at 2000 and 4000 ppm; NOEL = 200 ppm; no clear

target organ was identified; study was used to select doses for CDFA # 067846. ACCEPTABLE.
(Gee, 7/18/89).

034 021593 "Simazine 80W Safety Evaluation by Oral Administration to Dogs for 104 Weeks,"
(Woodard Research Corp., Herndon, VA, 3/9/64). Three dogs/sex/group were fed 0, 15, 150 or
1500 ppm for 2 years. Nominal NOEL \geq 1500 ppm. UNACCEPTABLE with insufficient information, no
adverse effect identified; No dose or diet analysis, no purity of test article, no clinical
observations., no age given, doses not justified and may not have been high enough. (J.
Gee, 5/1/85)

EPA 1-liner: Supplementary. No overt signs of toxicity at 1500 ppm. Chronic
toxicity and oncogenic potential could not be determined (too few animals) body weight
changes at 150 and 1500 ppm.

ONCOGENICITY, RAT

108 117094 An adverse effects disclosure statement was submitted by Ciba-Geigy (July 24,
1992). In the letter it was stated that in June of 1989, Ciba-Geigy initiated two new
oncogenicity studies on simazine using female Sprague-Dawley rats derived from the F2b
generation of the rat reproduction study (DPR document/record #: 213-103/096434). These
animals were exposed to simazine in utero and for 24 months post partum at dietary levels of
0, 10, 100 and 500 ppm. In addition, an age-matched group of control Sprague-Dawley females
was employed in the study. The following two separate studies were performed: **Study I:**
Treated and control rats were allowed to mate with untreated males, then delivered and nursed
the pups through lactation day 21. **Study II:** Animals in this group were treated the same as
those in Study I, except they were not mated. The in life portion of this study was completed
in June of 1991. The following results were observed after histological examination:

**Simazine Technical: Ovarian Neoplasia/Hyperplasia Incidence in Female
Sprague-Dawley Rats**

In Utero Exposure/Oncogenicity Study

Lesion/Tumor	Feeding Level (ppm)				
	0a	0b	10	100	500
<u>NULLIPAROUS FEMALES:</u>					
Hyperplasia (Sertoli Cells)	12/50	9/25	20/50	21/50	31/50
Sertoliiform Adenoma	0/50	0/25	0/50	1/50	5/50
<u>PRIMIPAROUS FEMALES:</u>					
Hyperplasia (Sertoli Cells)	17/50	7/25	14/48	14/47	28/49
Sertoliiform Adenoma	0/50	0/25	0/48	0/47	1/49

a - The test and control groups were derived from the F2b litter of the 2 generation reproduction study (DPR document/record #: 213-103/096434).

b - This control group was comprised of age-matched Sprague-Dawley females obtained from Charles River Laboratories.

The letter also stated that the incidence of ovarian tumors was not elevated in the combined study previously submitted and reviewed at DPR (DPR document/record #: 213-067/067849), in which animals were dosed up to 1000 ppm. Therefore, the ovarian findings in the two studies described above constitute a new potential adverse effect. M. Silva, 12/31/92 (No worksheet.)

ONCOGENICITY, MOUSE

** 066 067848 "Simazine Technical, 95-Week Oral Toxicity/Oncogenicity Study in Mice," (Ciba-Geigy Corporation, 4/4/88). Simazine technical, (Batch no.: FL 840988; purity = 96.5%)

was administered in diet to Crl:CD 1 (ICR) BR mice at 0 (90/sex/group), 40 and 1000 (80/sex/group), and 4000 (90/sex/group) ppm for 95 weeks. NOAEL \geq 4000 ppm. NOEL = 40 ppm (decrease in body weight gain, food and water consumption--observed in both sexes at 1000 and 4000 ppm; transitory increase in brain weight, relative brain, liver and kidney weights--females at 1000 and 4000 ppm and relative adrenal and heart weights--females at 4000 ppm; increase in relative lung and thyroid/parathyroid weights--females at 4000 ppm). There was no oncogenic effect observed with simazine. No adverse effect indicated. ACCEPTABLE. (M. Silva, 6/6/88, Gee, 7/19/89).

034 021592 "Carcinogenicity Study with Simazine Technical in Albino Mice." **Invalid IBT study.**

REPRODUCTION RAT

** 103, 110 096434, 122625 "Simazine Technical: Two-Generation Reproductive Toxicology Study in Rats", (D.L. Epstein, J.R. Hazelette, & E.T. Yau, Ciba-Geigy Corporation, Research Department, Pharmaceuticals Division, Laboratory Study No.: 882095, 2/12/91). Simazine Technical (purity 96.9%) was fed in diet to Sprague-Dawley rats (30/sex/group) at 0, 10, 100, or 500 ppm for two generations. Systemic Parental NOEL = 10 ppm based on decreased body weight gain and decreased food consumption in both sexes of both generations at \geq 100

ppm. Reproduction NOEL \geq 500 ppm (There were no reproductive effects at any dose.)
Originally reviewed as unacceptable (Kishiyama & Silva, 12/30/92), upon submission and review
of the requested information the study is now upgraded to acceptable. (M. Silva, 10/5/93).

034 021590 "Three-Generation Reproduction Study in the Rat," (Woodard Research Corp.,
9/14/65). Twenty per sex were fed 0 or 100 ppm, and 10 males plus 20 females were added in F1
matings at 50 ppm. Simazine at 80% but diets were adjusted to contain the nominal amount of
active ingredient (see 058) UNACCEPTABLE, no adverse reproductive effect identified. F0 not
necropsied. No food consumption, no individual pup weights, only 1 male and 1 female pup per
litter for histopathology from F3b. Dose selection not justified, no analyses of diets for
actual content. Reproductive NOEL \geq 100 ppm. (J. Gee, 5/1/85)

EPA 1-liner: This study was downgraded from Minimum to Supplementary due to a review
by H. Spencer 2/89 and the FRSTR review (March, 1989). NOEL > 100 ppm (HDT).

045 021590 Reviewed in volume 034.

TERATOLOGY, RAT

** 105 053580 "Simazine Technical: A Teratology Study in Rats," (Ciba-Geigy Corporation,
Summit, NJ, 4/7/86, Study #83058). Simazine technical (batch no F1-821846; purity = 98.2%)
was administered by gavage to mated (presence of sperm = day 0 of gestation) CRL COBS CD (SD)
(BR) rats at 0 (vehicle = 2.0% carboxymethylcellulose), 30, 300 and 600 mg/kg during days 6 to
15 of gestation, 25/group. Maternal NOEL = 30 mg/kg/day (decreased weight gain and food
consumption at 300 and 600 mg/kg/day. Developmental NOEL = 30 mg/kg/day (increase in head not
completely ossified, teeth not ossified, centrum/vertebra not ossified and rudimentary 14th
rib). Initially reviewed as having No adverse effect indicated and NOT ACCEPTABLE (no
analysis of dosing material) but upgradeable. (Y. Luthra, 10/87 and M. Silva, 6/23/88).
Document 213-073, record # 070893 contains the analyses of dosing solutions including
homogeneity and stability in the vehicle over 15 days. The study is upgraded to ACCEPTABLE
status. (Gee, 7/17/89).

EPA 1-liner: Core Grade is supplementary per review of D. Anderson 10/3/88.

073 070893 Analysis of dosing solutions for homogeneity and stability and content.
Upgrades CDFA # 053580. No worksheet. Gee, 7/18/89.

065 067847 Exact duplicate of 053580.

TERATOLOGY, RABBIT

** 044 020194 "A Teratology Study of Simazine Technical in New Zealand White Rabbits,"
(Ciba-Geigy, Summit, New Jersey, 3/29/84). Eighteen per group were given 0, 5, 75 or 200
mg/kg by gavage, days 7-19 of gestation. Test article at 97% purity. Maternal NOEL = 5 mg/kg
(decreased weight gain, anorexia, nervous tremors at 75 and 200 mg/kg). Developmental NOEL =
5 mg/kg (late resorptions at 75 and 200 mg/kg; reduced fetal weight at 200 mg/kg). ACCEPTABLE
with no adverse effect. (J. Gee, 5/2/85. M. Silva, 6/15/88).

EPA 1-liner: Supplementary. Maternal NOEL = 5 mg/kg (tremors, abortions, decreased
body weight gain and food consumption; fetotoxic NOEL = additional information required.

MUTAGENICITY, GENE MUTATION

Microbial Systems

** 068 067850 "Simazine Technical: Salmonella/Mammalian - Microsome Mutagenicity Assay
(Ames Assay)," (Ciba-Geigy Corporation, Greensboro, NC). Simazine technical (batch FL 850614;
purity = 96.9%) was used in the Ames test at 0 (vehicle = DMSO), 10, 25, 50, 100 and 250
ug/plate on Salmonella typhimurium strains: TA98, TA100, TA1535, TA1537 and TA1538 with and
without rat liver S-9. No mutagenicity was observed with any tester strain at any dose.
Positive controls functioned as expected. ACCEPTABLE. (M. Silva, 6/9/88).

042 020200 "Comparative Mutagenicity Studies with Pesticides," Summary of various mutagenicity screenings -UNACCEPTABLE with no effects noted.

050 038561-2 "In Vitro and In Vivo Microbiological Assays of Six Ciba-Geigy Chemicals," (SRI, 3/77) Salmonella, and host- mediated in mice. TA1535 TA1537, TA98 and TA100 at 0, 50, 100, 500, 5000 ug/plate +/- S9, 2 trials, 1 value per concentration: missing data, UNACCEPTABLE. No increase in revertants. Upgradeable when clarify number of plates and purity of test article. In 058, there is a statement that SRI has agreed to provide the additional information if available. (J. Gee, 2/20/86 and 11/6/87).

Mammalian systems

050 038566 "L5178Y/TK+ Mouse Lymphoma Mutagenicity Test." Ciba-Geigy, Basle, Switzerland, 5/7/84. Simazine, 99.6% lot #209158 at 1, 4, 8, 16, 32, 48, 64 and 80 ug/ml +/- rat liver S9, 5 hours; one trial, one culture/concentration, no increase in mutation frequency; precipitation at 40-80 ug/ml. UNACCEPTABLE, not upgradeable - no confirming trial. (J. Gee, 2/20/86)

MUTAGENICITY, CHROMOSOME ABERRATIONS

** 088 086391 "Structural Chromosomal Aberration Test Micronucleus Test, Mouse", (Dr. Carla Ceresa, Ciba-Geigy Limited, Basle, Switzerland, Laboratory Study no. 881189, 9/15/88). Technical simazine (G 27 692, purity = 99.6%) was administered in one oral dose (gavage) to 8 mice (Tif: MAGF, SPF)/sex/group. Part I: Harvest was at 16, 24 and 48 hours for control (0.5% Carboxymethyl cellulose) and simazine (5,000 mg/kg--limit test). Part 2: Harvest was at 24 hours for control (0.5% CMC) and simazine (1250, 2500, and 5,000 mg/kg--limit test) treatments. 1000 polychromatic and normochromatic erythrocytes each were scored/animal (5/sex/group) for micronucleus assessment. The PCE/NCE ratio/animal was determined by counting a total of 1000 erythrocytes. Polychromatic erythrocytes with micronuclei did not

increase relative to negative controls, after treatment with simazine. ACCEPTABLE.
(Kishiyama & Silva, 7/24/90).

** 068 067867 "Chromosome Studies on Human Lymphocytes in vitro," (Ciba-Geigy Limited, 3/24/88). Simazine technical (batch no. 209158; purity= 99.6%) was used on primary cultures of human lymphocytes for 3 hours at 0 (vehicle = DMSO), 6.25, 12.5, 25, 50, and 100 ug/ml with and without activation to test for chromosomal aberrations. No increase in chromosomal aberrations was observed with simazine-treated cells when compared to control. Positive controls functioned as expected. ACCEPTABLE. (M. Silva, 6/10/88).

042 020197. See 020196 in 844.

050 038564 "Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster," (Ciba-Geigy, Basle, Switzerland, 2/20/84) Simazine 99.6% technical at 0, 1250, 2500 and 5000 mg/kg, orally twice to 6/sex/group; 1000 cells in each of 3/sex/group were analyzed for micronuclei at 24 hours only after second dose. If the effect on cell cycling is not known (report gives no indication), animals should be sacrificed over 12-72 hours. Also, since the LD50 is >5000 mg/kg, dosing to toxic levels as required for the test might be difficult in which case the micronuclei test is not appropriate. No information on PCE/NCE or mitotic index is given. UNACCEPTABLE - inadequate protocol. No adverse effect. (J. Gee, 2/20/86)

058 no record # Rebuttal to #38564, Ciba-Geigy, 2/24/87: Indicated that the Ciba-Geigy lab in Basle, Switzerland was to provide the requested additional information by June 30, 1987.

MUTAGENICITY, DNA DAMAGE/REPAIR, MISC.

** 088 086392, "Tests for Other genotoxic Effects Autoradiographic DNA Repair Test on Rat Hepatocytes", (Dr. Thomas Hertner, Ciba-Geigy Limited, Basle, Switzerland, Laboratory Study No. 891412, 12/7/89). Simazine (G 27 692 technical; purity = 96.9%) at concentrations of 0

(DMSO or culture medium), 1.57, 4.72, 14.17, 42.5, 85 and 170 µg/ml were assayed with primary cultures of rat hepatocytes. Treatment period was for 16-18 hours in both the original and confirmatory tests. Analysis was performed by autoradiography (3 slides/dose, 50 cells were scored/slide). Simazine doses did not induce DNA damage to primary hepatocytes. Positive controls functioned as expected. ACCEPTABLE. (Kishiyama & Silva, 7/23/90).

042 020199 "Mutagenicity Screening of Pesticides in the Microbial System" (Mutation Research 10: 19-30 (1986)) Institute of Environmental Toxicology, Japan). Survey of 166 pesticides. No positive effect with simazine reported.

** 050 038563 "Autoradiographic DNA Repair Test on Rat Hepatocytes," (Ciba-Geigy, Basle, Switzerland, 12/20/83, report 830640.) Simazine, 99.6%, lot 209158; primary Rat hepatocytes exposed to 0, 0.4 2, 10 or 50 ug/ml for 5 hours in presence of 3H-TdR; No increase in UDS grains/nucleus. ACCEPTABLE. (J Gee, 2/20/86)

050 038565 "Autoradiographic DNA Repair Test on Human Fibroblasts," Ciba-Geigy, 12/20/83. Simazine, 99.6% technical, lot #209158; 0, 0.2, 1, 5 and 25 up/ml without activation for 5 hours; No increase in UDS reported fibroblasts CRL1121. UNACCEPTABLE - incomplete - no activation. (J. Gee, 2/20/86)

042 020196 "Evaluation of Selected Pesticides as Chemical Mutagens In Vitro and In Vivo Studies," Summary of 20 pesticide survey, UDS/gene conversion - No effects noted. (J. Gee, 5/2/85)

042 020198 See also 020196.

039093 to 039100 - various mutagenicity summaries.

****NOTE: EPA does not have record of review on any mutagenicity studies (842, 843 or 844), therefore there remain data gaps in all these areas for EPA.

NEUROTOXICITY

Not required at this time.